REMARKS

CLAIM AMENDMENTS

Claims 1 and 17 have been amended to recite that the dosage form is a tablet. Support for the amendments is found throughout the specification, for example, in paragraphs 0128, 0129, and 0130 of the instant specification. No new matter has been added to the application with the claim amendments set forth herein.

CLAIM REJECTIONS – 35 USC § 102

Claims 1-8, 10-13, 17, 18, and 26 stand rejected under 35 U.S.C. § 102(b) as anticipated by Franz et al. (USPN 5,232,704).

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently, in a single prior art reference. *Minn. Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1565, 24 USPQ2d 1321, 1326 (Fed. Cir. 1992). To be prior art under 35 U.S.C. § 102, the reference must put the anticipating subject matter into the possession of the public through an enabling disclosure. *Chester v. Miller*, 906 F.2d 1574 (Fed. Cir. 1990).

As recited in amended independent claim 1, the present invention relates to a method for selecting an optimized controlled release dosage form for administration to a patient such that the dosage form will have a predetermined drug release profile *in vivo*, the method comprising (a) preparing a plurality of different candidate dosage forms each comprised of a biocompatible, hydrophilic polymer and a pharmacologically active agent incorporated therein; (b) obtaining the *in vitro* drug release profile for each candidate dosage form in an aqueous medium in a USP disintegration tester; (c) comparing the *in vitro* drug release profiles obtained in (b), and determining which of the *in vitro* drug release profiles correlates most closely with a desired *in vivo* drug release profile; and (d) selecting the dosage form having the determined *in vitro* drug release profile for administration to a patient, wherein the dosage form is a tablet.

As recited in independent claim 17, the present invention also relates to a method for delivering a pharmacologically active agent to the upper gastrointestinal tract of a patient over an extended period of time while minimizing delivery to the lower gastrointestinal tract and colon, the method comprising orally administering to a patient in whom the fed mode has been induced

a sustained release oral dosage form comprised of a therapeutically effective amount of the pharmacologically active agent incorporated in a matrix of at least one biocompatible, hydrophilic polymer that (a) swells in the presence of water in gastric fluid such that the size of the dosage form is sufficiently increased to provide gastric retention of the dosage form in the stomach of a patient in whom the fed mode has been induced; (b) gradually erodes within the gastrointestinal tract over a determinable time period; and (c) releases the active agent throughout the determinable time period, wherein the dosage form is optimized by subjecting the dosage form to a disintegration test for an extended period of time such that the dosage form has an *in vitro* active agent release profile that correlates to a desired *in vivo* active agent release profile for the dosage form, and further wherein the dosage form is a tablet.

Franz et al. discloses and claims a capsule including a non-compressed bi-layer formulation for sustained release administration of pharmaceuticals. Franz et al. does **not** teach or suggest how to modify the capsule to a tablet dosage form. Because Franz et al. does not teach or suggest a tablet dosage form, Franz et al. does not anticipate the claimed invention. Accordingly, applicants respectfully request withdrawal of this rejection.

CLAIM REJECTIONS – 35 USC § 103

Claims 1-26 stand rejected under 35 USC § 103(a) as obvious over Shell et al. (US 5,972,389) in view of discussion in paragraph 0005 of the Background section of applicant's patent application. This rejection is respectfully traversed.

When establishing a *prima facie* case of obviousness, the Office must show that the cited prior art references, either singly or in combination, suggest the desirability of the claimed subject matter. *In re Deminski,* 796 F.2d 436, 230 USPQ 313 (Fed. Cir. 1986). Improper hindsight analysis is the reading into the art of the applicant's own teachings. *Id.*

Shell et al. teaches a gastric retentive oral dosage form that is tested with USP dissolution test equipment. Shell et al. does ***not*** teach or suggest using the disintegration test on controlled release dosage forms. At page 4 of the Office Action dated March 8, 2005, the Examiner acknowledges that Shell et al. does not disclose testing disintegration of the dosage form.

The Examiner cites paragraph 0005 of the instant application to remedy the deficiencies of Shell et al. Paragraph 0005 of the application explains Section 701 of USP 24 – NF 19, which

is attached. Section 701 of the USP describes the procedures for Disintegration Testing. The first sentence explains that the test described is used to determine compliance with the limits on disintegration stated in the monographs. Section 701 is clear that the test is **not** to be used with modified-release dosage forms, which implies that the test is used only for immediate release dosage forms.

Contrary to the Examiner's statement at the bottom of page 4 of the present Office Action, paragraph 0005 does **not** teach that the dissolution test can supplement the disintegration test; rather, this paragraph merely explains the existence of the disintegration test for testing the limits of disintegration for immediate release dosage forms. The statement in paragraph 0005 that the disintegration test "is conventionally used to supplement dissolution" is solely in reference to the use of the disintegration test ***to predict in vivo release profiles***; the statement is ***not*** saying that the disintegration test is being used in addition to the dissolution test.

As previously noted, Shell et al. teaches that a dissolution test can be used for controlled-release dosage forms. The disclosure in applicant's paragraph 0005 citing USP 24-NF 19 § 701 indicates that the disintegration test can be used for immediate release dosage forms, but not for modified release dosage forms, a subset of which is controlled release dosage forms. Based on the hypothetical combination of Shell et al. and paragraph 0005, the only conclusions that the ordinary artisan could draw from the teachings of these two references is that the dissolution test is to be used to predict in vivo release profiles for controlled release dosage forms and the disintegration test is to be used to predict in vivo release profiles for immediate release dosage forms. In view of the foregoing, the only way that the ordinary artisan could arrive at the claimed invention using the teaching of Shell et al. in view of paragraph 0005 would be to apply the disclosure of the instant application that the disintegration test is used to predict in vivo release profiles of controlled dosage forms, which would of course be an impermissible hindsight reconstruction. In this respect, the Examiner cannot then use the disclosure of the present invention in the patent application at issue to conclude that the disintegration test can be used with controlled release dosage forms. *In re Deminski, supra.*

In addition to the foregoing, applicants repeat the argument from the previous response that the inventors achieved the claimed invention by doing what those skilled in the art suggested should not be done, specifically to predict in vivo release profiles for a controlled release dosage

form using a disintegration test, which, according to well-established Federal Circuit law, is a fact strongly probative of nonobviousness. *Kloster Speedsteel AB v. Crucible, Inc.,* 793 F.2d 1565, 230 USPQ 81 (Fed. Cir. 1986), *on rehearing,* 231 USPQ 160 (Fed. Cir. 1986). As noted in paragraph 0005 of the instant application, Section 701 provides that disintegration tests are not to be used for modified release dosage forms. In direct opposition to this teaching, applicant's invention is to the use of disintegration testing with controlled release dosage forms, which are a subset of modified release dosage forms.

With respect to the Examiner's assertion that the applicants have not shown unexpected results, the Examiner is directed to review Example 1, and Figures 1 and 2 of the instant specification, which indicate the benefits of testing controlled release dosage forms using the disintegration test. Example 1 outlines a protocol for testing a controlled release dosage form using the disintegration test in comparison to the dissolution test. Figures 1 and 2 indicate that the results yielded from the disintegration test were closer to the in vivo results than were results from a dissolution test, and therefore more predictive of performance of the controlled release dosage form in vivo (see specification paragraph 0153). Along similar lines, it is readily apparent from the graphs in Figures 1 and 2 that the disintegration and dissolution tests for the same dosage form do not agree. Paragraphs 0154 and 0155 of the instant specification explain that there is a significant difference between dissolution results and disintegration results for the same dosage form and that dissolution apparatus should only be used as a quality control tool to characterize the dosage form.

As the foregoing demonstrates, Shell et al. in view of paragraph 0005 does not render the claimed invention obvious; accordingly applicants respectfully request withdrawal of this rejection.

THE PROVISIONAL DOUBLE-PATENTING REJECTION

Claims 1-3 stand provisionally rejected under 35 U.S.C. § 101 over claims 49-51 of U.S. Patent Application Serial No. 10/281,284. As applicants have cancelled claims 49-51 of U.S. Patent Application Serial No. 10/281,284, this rejection is rendered moot. In light of the foregoing, applicants respectfully request withdrawal of this rejection.

CONCLUSION

The foregoing amendments and remarks address all issues of anticipation, obviousness, and double patenting set forth by the Examiner in the pending Office Action; accordingly, upon entry of this response, there will be no outstanding issues in this application. In light of the foregoing, applicants respectfully request reversal of all outstanding rejections and passage of this application to allowance.

If the Examiner has any questions regarding this Amendment that may be addressed by way of a telephone call or e-mail correspondence, she is encouraged to contact the undersigned at 650-251-7707 or firestone@reedpatent.com.

Respectfully submitted,

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Attachment: USP 24-NF 19 § 701
For USSN 10/773,986
Attorney Docket No. 3100-0003.10
Amendment Under 37 C.F. R. § 1.114
Dated November 28, 2005

<701> DISINTEGRATION

This test is provided to determine compliance with the limits on *Disintegration* stated in the individual monographs except where the label states that the tablets or capsules are intended for use as troches, or are to be chewed, or are designed as modified-release dosage forms (see *Drug Release* <724>). Determine the type of units under test from the labeling and from observation, and apply the appropriate procedure to 6 or more dosage units.

For the purposes of this test, disintegration does not imply complete solution of the unit or even of its active constituent. Complete disintegration is defined as that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus is a soft mass having no palpably firm core.

APPARATUS

The apparatus consists of a basket-rack assembly, a 1000-mL, low-form beaker, 138 to 155 mm in height and having an inside diameter of 97 to 110 mm for the immersion fluid, a thermostatic arrangement for heating the fluid between 35° and 39°, and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 29 and 32 cycles per minute through a distance of not less than 5.3 cm and not more than 5.7 cm. The volume of the fluid in the vessel is such that at the highest point of the upward stroke the wire mesh remains at least 2.5 cm below the surface of the fluid and descends to not less than 2.5 cm from the bottom of the vessel on the downward stroke. The time required for the upward stroke is equal to the time required for the downward stroke, and the change in stroke direction is a smooth transition, rather than an abrupt reversal of motion. The basket-rack assembly moves vertically along its axis. There is no appreciable horizontal motion or movement of the axis from the vertical.

Basket-Rack Assembly— The basket-rack assembly consists of six open-ended transparent tubes, each 7.75 ± 0.25 cm long and having an inside diameter of 20.7 to 23 mm and a wall 1.0 to 2.8 mm thick; the tubes are held in a vertical position by two plastic plates, each 8.8 to 9.2 cm in diameter and 5 to 7 mm in thickness, with six holes, each 22 to 26 mm in diameter, equidistant from the center of the plate and equally spaced from one another. Attached to the under surface of the lower plate is a woven stainless steel wire cloth, which has a plain square weave with 1.8- to 2.2-mm mesh apertures and with a wire diameter of 0.63 ± 0.03 mm. The parts of the apparatus are assembled and rigidly held by means of three bolts passing through the two plastic plates. A suitable means is provided to suspend the basket-rack assembly from the raising and lowering device using a point on its axis.

The design of the basket-rack assembly may be varied somewhat provided the specifications for the glass tubes and the screen mesh size are maintained.

Disks— The use of disks is permitted only where specified in the monograph. If specified in the individual monograph, each tube is provided with a cylindrical disk 9.5 ± 0.15 mm thick and 20.7 ± 0.15 mm in diameter. The disk is made of a suitable, transparent plastic material having a specific gravity of between 1.18 and 1.20. Five parallel 2-mm holes extend between the ends of the cylinder. One of the holes is centered on the cylindrical axis. The other holes are centered 6 mm from the axis on imaginary lines perpendicular to the axis and parallel to each other. Four identical trapezoidal-shaped planes are cut into the wall of the cylinder, nearly perpendicular to the ends of the cylinder. The trapezoidal shape is symmetrical; its parallel sides coincide with the ends of the cylinder and are parallel to an imaginary line connecting the centers of two adjacent holes 6 mm from the cylindrical axis. The parallel side of the trapezoid on the bottom of the cylinder has a length of 1.6 mm, and its center lies at a depth of 1.8 mm from the cylinder's circumference. The parallel side of the trapezoid on the top of the cylinder has a length of 9.4 ± 0.2 mm, and its center lies at a depth of 2.6 ± 0.1 mm from the cylinder's circumference. All surfaces of the disk are smooth. If the use of disks is specified in the individual monograph, add a disk to each tube, and operate the apparatus as directed under *Procedure*.

PROCEDURE

Uncoated Tablets— Place 1 tablet in each of the six tubes of the basket and operate the apparatus, using water maintained at 37 ± 2° as the immersion fluid unless otherwise specified in the individual monograph. At the end of the time limit specified in the monograph, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Plain Coated Tablets— Apply the test for *Uncoated Tablets*, operating the apparatus for the time specified in the individual monograph.

Delayed-release (enteric coated) Tablets— Place 1 tablet in each of the six tubes of the basket and, if the tablet has a soluble external coating, immerse the basket in water at room temperature for 5 minutes. Then operate the apparatus using simulated gastric fluid TS maintained at 37 ± 2° as the immersion fluid. After 1 hour of operation in simulated gastric fluid TS, lift the basket from the fluid, and observe the tablets: the tablets show no evidence of disintegration, cracking, or softening. Operate the apparatus, using simulated intestinal fluid TS maintained at 37 ± 2° as the immersion fluid, for the time specified in the monograph. Lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Buccal Tablets— Apply the test for *Uncoated Tablets.* After 4 hours, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Sublingual Tablets— Apply the test for *Uncoated Tablets.* Observe the tablets within the time limit specified in the individual monograph: all of the tablets have disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Hard Gelatin Capsules— Apply the test for *Uncoated Tablets.* Attach a removable wire cloth, which has a plain square weave with 1.8- to 2.2-mm mesh apertures and with a wire diameter of 0.60 to 0.655 mm, as described under *Basket-rack Assembly*, to the surface of the upper plate of the basket-rack assembly. Observe the capsules within the time limit specified in the individual monograph: all of the capsules have disintegrated except for fragments from the capsule shell. If 1 or 2 capsules fail to disintegrate completely, repeat the test on 12 additional capsules: not less than 16 of the total of 18 capsules tested disintegrate completely.

Soft Gelatin Capsules— Proceed as directed under *Hard Gelatin Capsules*.